Lesch-Nyhan Syndrome

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LNS is a genetic disorder caused by a mutation in the HRPT(1) gene of the X-chromosome. This mutation results in deficient production of hypoxanthine guanine phosphoribosyltransferase, an enzyme that is vital in metabolizing Vitamin B₁₂ and recycling purines¹.

The condition Affects 1 in 380,000 People
LNS is characterized by the following

- Cognitive and Behavioral Disturbances
  - LNS’s infamous symptom is persistent self-mutilation
    - Such as biting fingers, lips and banging one’s skull or limbs
- Delayed Development
- Onset of Huntington Disease-like symptoms
  - Facial grimacing, repetitive involuntary leg/arm movements and involuntary writhing
- Low Muscle Tone (Hypertonia)
- Overproduction of Uric Acid (Hyperuricemia)
  - This is a side effect of being unable to recycle purines
- Motor Dysfunction (≈ Similar to that of Cerebral Palsy)
- In most cases, an inability to walk from childhood
Nervous System Dysfunctions include

- Mental retardation
- Spasticity (Lack of Muscle Inhibition)
- Hyperreflexia (Exaggerated Reflexes)
- Opisthotonus (Bridging formation of the head, spine and neck)
- Dysarthria (Motor Speech Disorder)
- Dysphagia (Swallowing Problems)
- Mental retardation
Living with LNS

Living With Lesch-Nyhan: The Story of Bill
Diagnosing LNS

- Check phenotype (cognitive, behavioral or neurological) indications of Lesch-Nyhan Syndrome
- Confirmed through a series of diagnostic tests:
  - Urate v. Creatinine Ratio > 2.0 is characteristic of LNS
  - 24-Hour Urate Excretion > 20mg/kg is also characteristic
- HPRT(1) Enzyme Activity
  - Males: HPRT Activity < 1.5% in cells is diagnostic
  - Females: Technically demanding and some inaccuracies
- Proliferation of Blood T-lymphocytes: blood test available on a research basis only

Though used in initial diagnosis, these tests aren’t considered diagnostic.
Diagnosing LNS: Molecular Genetic Testing

- **Sequence Analysis/Mutation Scanning:**
  - Using multiple methods to screen DNA to find the locus that has a variant gene; >90% accuracy in affected males; ≈ 80% in carrier females.

- **Deletion/Duplication Analysis:**
  - Analyzes the 20-24% of HPRT(1) large deletions in females that are undetectable in Sequence Analysis.

- **Prenatal and Carrier Testing**
  - Search for the presence of a Purine analolgue
A Clinical Synopsis

- LNS is X-Linked and therefore has 100% Genetic Penetrance in Males
- Female carriers are usually asymptomatic, rarely showing any symptoms of the disorder

- The Deficient HPRT enzyme (as a consequence of mutation) has very limited functionality in a LNS patient

- In general, life expectancy caps at the 2\textsuperscript{nd} or 3\textsuperscript{rd} decade of life

- Finger biting is a \textit{behavioral phenotype}\textsuperscript{3} for LNS, often serving to distinguish from other self-injurious prone conditions (i.e. Tourette syndrome and other psychiatric conditions).

- Overproduction of Uric Acid (also, inability to recycle the acid) may lead to deposits in kidneys, bladders or ureters
  - Causing sever kidney problems and exacerbating joint swelling (\textit{Gout})
Bill’s ordeal epitomizes the nature of treatment for Lesch-Nyhan Syndrome

- The disease is dealt with symptomatically, since there is no cure for the condition itself
- Physical therapy as well as medicinal treatment specific to the patient
- Essentially a multidrug approach to treating LNS
- Gout Medication (Allopurinol) for decreasing uric acid levels
- “Some may be relieved with the drugs carbidopa/levodopa, diazepam, phenobarbital, or haloperidol” (NINDS).
1 – Purines: aromatic, organic compounds that are biochemically significant components in a number of other important biomolecules

3 – Here is an interesting article on a deletion mutation associated with HPRT(1).

4 – Behavioral Phenotype: A characteristic pattern of motor, cognitive, linguistic and/or social abnormalities which is consistently associated with a biological disorder.

New Yorker Article on LNS
Works-Cited

- http://www.dmid.org/clinchap3.htm